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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/805,761	03/13/2001	Parkash S. Gill	21327-0701CON2	4201

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EXAMINER	
MCGARRY, SEAN	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 12/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/805,761	GILL ET AL.	
	Examiner	Art Unit	
	Sean R McGarry	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *15-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-14 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Uchida et al [US 6,150,092] in view of Robinson [WO 95/04142, cited by applicant], Agrawal et al [PNAS Vol. 94: 2620-2625, 1997, cited by applicant] and Bennett et al [US 5,998,148].

Uchida et al have taught antisense and pharmaceutical compositions comprising antisense targeted to VEGF. Uchida et al have also taught the inhibition of VEGF in a subject via antisense nucleic acids targeted to VEGF (see claims 18-25, for example). In particular Uchida et al have taught antisense targeted to SEQ ID NO: 7 of VEGF and have taught numerous specific oligonucleotides targeted to SEQ ID NO: 7 such as SEQ ID NOS: 51, 54, 53, 50, 49, 38, and 41 (see claims 1-16, for example). It has been taught by Uchida et al that inhibition of VEGF results in the inhibition of solid tumor growth (see column1, for example) and have taught that if VEGF is present in the tumor it is subject to VEGF inhibitory treatment. It has been taught that the development of

antisense oligonucleotides to VEGF replaces the methodology of inhibiting VEGF in tumors with antibodies (see column 2, for example). Columns 4-5 discuss how one in the art can use known oligonucleotide modifications in VEGF antisense oligonucleotides, for example. At columns 7-8 it is taught that various kinds of cancer can be treated with VEGF directed antisense molecules. At column 27 it has been taught that VEGF antisense oligonucleotides can be used to inhibit the growth of solid tumors via the inhibition of VEGF which inhibits angiogenesis which in turn inhibits the growth of solid tumors, for example.

The antisense oligonucleotides claimed by Uchida et al are targeted, for example, to the specific region of VEGF nucleic acid SEQ ID NO: 7. It is noted that antisense oligonucleotides of the instant application, including claimed SEQ ID NO: 34 (modified version of SEQ ID NO:2) as well as SEQ ID NOS: 2, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 28, and 29, for example, are all targeted to SEQ ID NO: 7 of Uchida et al, and further all the antisense oligonucleotides of the instant application either overlap, embrace, or are embraced by the specifically claimed antisense of Uchida et al claim 7, for example (SEQ ID NOS: 51, 54, 53, 50, 49, 138, and 141 of Uchida et al, for example). It is clear that the antisense oligonucleotides claimed by Uchida et al reasonably be expected to have an IC50 value of between about 0.5 and 2.5 micromolar, especially since the claims (i.e. 4, 5, 12, 13) do not require any particular conditions to ascertain an IC50 value, for example. Finally Uchida et al have taught that that region of VEGF SEQ ID:7 is a "core region" (see column 21-22) and further teach at column 26 that "[I]n view of the role of VEGF as a tumor angiogenic

factor in vivo [citations omitted], the antisense nucleic acid having a nucleic acid sequence complementary to 8 or more nucleotides in the core region is useful as a therapeutic agent such as anticancer drug to inhibit the growth of solid tumors or a a diagnostic agent for cancers."

Uchida et al do not teach the 2'O-methyl modifications of SEQ ID NO: 34, the specific cells of claim 7, chemotherapeutic agents included in a composition comprising a VEGF antisense or the use of liposomes in the delivery of an antisense VEGF composition.

Robinson et al have taught the inhibition of VEGF to inhibit tumor angiogenesis (see page 4, for example). It has been taught at pages 7-8 that modifications to antisense nucleic acids are desirable to prevent attach by nucleases, for example, and it has been taught specifically, at pages 8-9, for example) the modification of an antisense oligonucleotide to comprise oligonucleotides that comprise an unmodified internal sequence that is flanked on the 5' and 3' termini by modified nucleic acid sequences.

Agrawal et al have taught the same modification used in SEQ ID NO: 34 in Table 1, for example. It has been taught that this oligonucleotide has nuclease resistance, for example.

Bennett et al have taught many available modifications available to one in the art at the time the invention was made and this includes hybrid, mixed and gapmer oligonucleotides which all relate to an antisense oligonucleotide comprising an RNase substrate region between modified portions of an oligonucleotide, where the modification(s) provide for increased nuclease protections and/or better substrate

affinity, for example (see columns 6-10 and particularly Example 5, for example). At columns 12-13 it has been taught the numerous available compositions and delivery vehicle available for one in the art at the time of invention including the use of liposome formulations for the delivery of antisense oligos to a patient, for example.

One in the art would clearly have had motivation to make the instantly claimed antisense molecules since it is absolutely clear that the region targeted (core region SEQ OID NO:7 of Uchida et al) has been clearly shown by the prior art to be a desired target for antisense inhibition of VEGF where Uchida et al have taught that one in the art would expect antisense oligonucleotide so targeted to inhibit VEGF in solid tumors. Furthermore the specific antisense is not only targeted to the taught target sequence but overlaps, embrace or are embraced by the specific VEGF antisense taught by Uchida et al where the instant application has shown that antisense targeted thereto would be expected to have an IC50 value recited in the claims (ie the IC50 value is an observed property of antisense targeted to this core region of VEGF, for example).

**[A REFERENCE TEACHING PRODUCT APPEARING TO BE SUBSTANTIALLY IDENTICAL IS MADE THE BASIS OF A REJECTION,
AND THE EXAMINER PRESENTS EVIDENCE OR REASONING TENDING TO SHOW INHERENCY, THE BURDEN SHIFTS TO THE
APPLICANT TO SHOW AN UNOBVIOUS DIFFERENCE**

"[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. *In re Fitzgerald,* 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting *In re Best,* 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)).]

One in the art would clearly look to this specific region to make antisense oligonucleotides to inhibit VEGF since this specific region and antisense thereto have

been clearly taught in the art to be effective antisense oligonucleotides and target sequence. One would expect that the inhibition conditions recited in the claims would be met since these values were observed upon making antisense targeted to the specific region clearly taught in the prior art. One would have been motivated to make the modification specifically as in instant SEQ ID NO: 34 since this type of modification was clearly taught in the art as one of many modifications one in the art could choose to increase nuclease stability or to increase target affinity, for example. Bennett et al have clearly shown that liposome delivery is one of a number of methods one in the art could have chosen to deliver an antisense to a subject. One would clearly have chosen any of the vast range of solid tumors where VEGF is expressed since it is clear from the teachings of Uchida et al and Robinson that any tumor expressing VEGF is clearly a target for antisense VEGF therapy. In regard to claims 2, 3, the following is noted:

"It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be prima facie obvious.). See also In re Crockett, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components

individually promote the formation of a nodular structure in cast iron.); and Ex parte Quadranti, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held prima facie obvious). But see In re Geiger, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987) ("Based upon the prior art and the fact that each of the three components of the composition used in the claimed method is conventionally employed in the art for treating cooling water systems, the board held that it would have been prima facie obvious, within the meaning of 35 U.S.C. 103, to employ these components in combination for their known functions and to optimize the amount of each additive....Appellant argues... hindsight reconstruction or at best,... obvious to try'.... We agree with appellant.").

The invention as a whole would therefore have been *prima facie* obvious to one in the art at the time the invention was made.

Applicant's arguments filed 8/8/2003 have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant argues that the specifically recited oligonucleotide SEQ ID NO: 34 as modified is not obvious. Applicant requests that the examiner refrain from ad hoc comments on the patentability of unclaimed embodiments. It is noted that the comments of the examiner are made to demonstrate the fact that the region targeted by SEQ ID NO:34 is a popular and clear effective region to target as evidenced by the targeting of the region by the prior art and applicant, for example. The examiner has not made any comments as to the patentability of unclaimed embodiments. The examiner clearly would not wish to waste applicants or his time with rejecting inventions not claimed. Applicant asserts that the region taught by Uchida would not provide an art recognized meaningful predictive value. Applicant argues "GC" content calculations as evidence for the lack of meaningful predictive value of the Uchida et al reference. The examiner declines applicants invitation to further check the simple, yet laborious calculations of applicant since, applicant has not provided the calculations to be checked, and further since the argument of the "GC" content of the oligonucleotides of Uchida is greatly off point. Applicant compares apples and oranges. Why has applicant not considered only those oligonucleotides of Uchida et al that are targeted to the same region as the instant SEQ ID NO: 34? Since SEQ ID NO:34 is targeted to within the same region defined as SEQ ID NO:7 in Uchida it would appear only logical to make such a comparison instead of applicants comparison of all of the oligonucleotides of Uchida et al targeted to the entirety of VEGF and comparing that to applicants SEQ ID NO:34 which is targeted to a region of only tens of nucleotides. It would seem to one of ordinary skill in the art that the target sequence would dictate the GC content of the oligonucleotides targeted

thereto, especially when the target region is as small as in the instant invention and that taught by Uchida et al (SEQ ID NO:7 covers only 42 nucleotides). Applicant argues that Uchida's cell-free assay was nearly useless as a predictor of effectiveness in a cellular setting. This position is confusing since Uchida's methods show that the region defined by SEQ ID NO: 7 was a core region desirable for targeting antisense and this same region is where applicants target antisense. Applicant argues that the effectiveness of Uchida's SEQ ID NO: 51 and 47 as phosphorothioates. Again it is unclear what is applicants point. The antisense work. Applicant has not shown that their antisense under the same conditions as Uchida, function unexpectedly better or that Uchida's under those of applicants are unexpectedly poor, for example. Applicant attacks the methods of Uchida, but fails to specifically point out how each and every "shortcoming in Uchida" is avoided or addressed by applicant own disclosure. Applicant argue phosphorothioate of Uchida et al but applicants specification fails to show the activity of all of their oligonucleotides in an unmodified state, for example. Clearly one in the art would have looked to the region disclosed by Uchida et al to **optimize** antisense targeted to that same region. Applicant again is directed to the following.

> **A REFERENCE TEACHING PRODUCT APPEARING TO BE SUBSTANTIALLY IDENTICAL IS MADE THE BASIS OF A REJECTION,AND THE EXAMINER PRESENTS EVIDENCE OR REASONING TENDING TO SHOW INHERENCY, THE BURDEN SHIFTS TO THE APPLICANT TO SHOW AN UNOBVIOUS DIFFERENCE**
>
> **"[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. *In re Fitzgerald,* 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting *In re Best,* 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)).**

MPEP 2112.01:

PRODUCT AND APPARATUS CLAIMS – WHEN THE STRUCTURE RECITED IN THE REFERENCE IS SUBSTANTIALLY IDENTICAL TO THAT OF THE CLAIMS, CLAIMED PROPERTIES OR FUNCTIONS ARE PRESUMED TO BE INHERENT

Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433.

COMPOSITION CLAIMS - IF THE COMPOSITION IS PHYSICALLY THE SAME, IT MUST HAVE THE SAME PROPERTIES

"Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990)

Applicant has argued that the Agrawal reference teaches away from modifying an antisense as is SEQ ID NO:34 and argues that Bennett does not help. Applicant merely states that Bennett does not correct the "defects in the other art" but fails to provide any reasons at all why. Regardless of this, it is clear that the Agrawal reference clearly provides motivation and a reasonable expectation of success to modify an antisense as is SEQ ID NO:3. It is noted that the rejection of record asserts that the prior art has taught that the modifications provide at least benefits of nuclease stability which in itself is clearly a motivation to modify for the *in vivo* use of an oligo. Applicant asserts that oligonucleotide NO:9 in Agrawal et al was not further tested and provide several baseless conjectures as to why. Upon a reading of the reference, however, it is clear that this modification was tested earlier by the authors and it was found that

"[I]ncorporation of these modified segments [2'-O-methyl] at the ends of PS-oligos (oligos 9 and 10) significantly improved their in vivo stability, safety profile, and biological activity as an antisense agent, and the oligos were absorbed after oral administration in rats (citation ommited)." If anything the examiner understated the benefits of such modifications. (see page 2624, lines 10-19).

It is applicants burden to provide evidence of an unobvious difference between the prior art and that instantly claimed. It appears from the rejection and arguments set forth above that applicant has merely optimized an antisense targeted to a clearly defined target region of only 42 nucleotides with a well known antisense modification.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean R McGarry whose telephone number is (703)305-7028. The examiner can normally be reached on M-Th (6:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

srm